Editorial Commentary

Clinical insights: five-year follow-up of KEYNOTE-189 trial outcomes and more

Bobby Se[1], Athar Eysa[2], Nagla Karim[3]

[1]Department of Internal Medicine, Inova Fairfax Hospital, Inova Health System, Falls Church, VA, USA; [2]Department of Internal Medicine, Morristown Medical Center, Atlantic Health System, Morristown, NJ, USA; [3]Department of Hematology and Oncology, Inova Schar Cancer Institute, Fairfax, VA, USA

Correspondence to: Nagla Karim, MD, PhD. Department of Hematology and Oncology, Inova Schar Cancer Institute, 8081 Innovation Park Dr, Fairfax, VA 22031, USA. Email: Nagla.Karim@inova.org.

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Study summary

KEYNOTE-189 is a randomized phase 3 study that compared the overall survival (OS) and progression-free survival (PFS) of pembrolizumab in combination with pemetrexed, and a platinum *vs.* standard of care pemetrexed and platinum in patients with advanced non-small cell lung cancer (NSCLC) (1). Six hundred and sixteen patients were randomized to receive either 200 mg of pembrolizumab or saline placebo, to be administered intravenously every 3 weeks for up to 35 cycles (1). Patients would receive 4 cycles of investigator choice of cisplatin (75 mg per square meter of body-surface area) or carboplatin (area under the concentration-time curve, 5 mg per milliliter per minute) and pemetrexed (500 mg per square meter) followed by pemetrexed every 3 weeks (1). All were to be administered intravenously.

The most notable inclusion criteria for this study included patients who are 18 years or older with pathologically confirmed metastatic NSCLC without target mutations who did not receive previous systemic therapy for their metastatic disease (2). Some notable exclusion criteria were for patients with a known history of human immunodeficiency virus (HIV), and active hepatitis B or C (2).

Data was analyzed at the one-year mark and was followed up after five years. The estimated OS at 12 months was 69.2% in the pembrolizumab arm *vs.* 49.4% in the placebo arm (3). The median PFS was 8.8 months in the pembrolizumab arm compared to 4.9 months in the placebo arm (3). At the 5 years follow-up, these results were maintained. The 5-year OS rates were 19.4% *vs.* 11.3% and the 5-year PFS rates were 7.5% *vs.* 0.6% (3). These results concluded that patients with metastatic non squamous non-small lung cancer without targetable mutations who were treated with pembrolizumab along with pemetrexed and a platinum-based drug showed improved OS and PFS when compared to a saline placebo along with pemetrexed and a platinum-based drug.

Critiques, praises and relevance to other studies

KEYNOTE-042 compared first-line pembrolizumab monotherapy with chemotherapy for patients with programmed death-ligand 1 (PD-L1) positive NSCLC using a PD-L1 tumor proportion score (TPS) cutoff of 1%. It showed a benefit with improved OS in the pembrolizumab arm, with a median OS of 16.7 *vs.* 12.1 months. In an exploratory subset analysis of patients with a PD-L1 TPS 1% to 49%, there was not a clear difference between pembrolizumab and chemotherapy (4). KEYNOTE-189 has established a role in pembrolizumab when used in subset population of patients with a TPS score between 1% to 49% (5) which is a unique study outcome not entirely analyzed in KEYNOTE-042. It is also apparent that

benefits were observed in the PD-L1 TPS <1% subgroup, for whom pembrolizumab monotherapy is not indicated (5). Therefore, supporting pembrolizumab's superiority in treatment of advanced NSCLC when used in combination with chemotherapy or as a single agent in patients with PD-L1 >1%.

Another critique of KEYNOTE-189 was the lack of diversity in its subset populations. This study has excluded patients with known history of HIV and hepatitis B virus (HBV), making it hard to apply the results to this subset of patients. The exclusion of patients with HIV has been the norm in clinical trials of cancer drug development (6). Most randomized clinical trials focus on the internal validity which likely explains this exclusion. However, the food and drug administration has approved PD-L1 checkpoint inhibitors in many HIV-associated cancers including NSCLC (7). Amongst HIV patients with lung cancer, NSCLC appears to be the most prevalent (8). That reflects the importance of developing clinical trials with criteria to include patients with HIV and optimize the NSCLC treatment in that category.

Another inclusion criterion of the study was an absolute neutrophil count of 1,500 or above (1). The study did not specify the ethnic stratification of patients in the demographics section. Benign ethnic neutropenia is common in African Americans, and it does not increase their risk for systemic infections (9). Based on this inclusion criterion, it is a high possibility that African Americans were not represented in the study demographics. Given that NSCLC is common in African Americans and, in fact, African American men have higher incidence of NSCLC than White men and by excluding this category, results cannot be generalized to this subset of patients (10).

KEYNOTE-189 also excluded patients with activating alterations such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK). Another trial, IMpower 150 that compared PFS and OS between different combinations of agents between atezolizumab (PD-L1 monoclonal antibody) and/or bevacizumab (a vascular endothelial growth factor inhibitor) with a carboplatin and paclitaxel backbone did include NSCLC with driver mutations such as EGFR and ALK (11). A head-to-head comparison between KEYNOTE-189 and IMpower 150 with patients with liver metastasis from NSCLC could provide more nuance in treatment selection.

Pembrolizumab has become part of the 1st line treatment of choice for advanced NSCLC. KEYNOTE-189 has further emphasized the importance of PD-L1 as a leading predictive biomarker for immune checkpoint inhibitor therapy. Adding immune check point inhibitor therapy has improved clinical outcomes in NSCLC and continues to be a novel therapy in oncology. While this clinical trial has demonstrated pembrolizumab's positive impact on NSCLC, there are still clinical questions that remain unaddressed. Although this trial has established pembrolizumab's role in NSCLC patients with a TPS score between 1% and 49%, it cannot be concluded from this study if pembrolizumab combined with chemotherapy is superior to pembrolizumab monotherapy in this subset population. This same analysis can be made for the subset population with a TPS score of less than 1%. Another unaddressed clinical question in this study is the safety profile for using pembrolizumab in patients with NSCLC who have a TPS score of less than 1%.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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